Docket No.: S2037-700210

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Bradley et al
Serial No.:	09/839,658
Confirmation No:	9914
Filed:	April 19, 2001
For:	NOVEL COMPOSITIONS AND METHODS FOR ARRAY-BASED NUCLEIC ACID HYBRIDIZATION
Examiner:	Teresa E. Strzelecka
Art Unit:	1637

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. §1.8(a)

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/Sandra Szela Congdon/
Sandra Szela Congdon

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APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

This Reply Brief is submitted in response to the Examiner's Answer mailed June 24, 2008 in the above-referenced patent application.

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I. Reply Brief Identification

Appellants:	Allan Bradley et al
Serial No.:	09/839,658
Filing Date:	April 19, 2001
Title:	Novel Compositions and Methods for Array-Based Nucleic Acid Hybridization
Examiner:	Teresa E. Strzelecka
Art Unit:	1637
Title of the Paper:	Reply Brief

II. Status of Claims (37 C.F.R. § 41.37(c)(1)(iii))

Claims 1-66 were originally filed with this case. Claims 18-66 were cancelled in response to a Restriction Requirement mailed on May 31, 2002. New claims 67-68 were added in response to an Office Action dated August 19, 2002. Claims 15-16 were canceled in response to an Office Action dated January 22, 2004. New claims 69-72 were added in response to an Office Action dated February 2, 2005. Claim 69 was canceled in response to an Office Action dated October 18, 2005. Claims 1-14, 17, 67, 68, and 70-72 are pending in this application, of which claim 1 is an independent claim. Each of these claims was rejected in a Final Office Action dated July 11, 2006. Claims 70 and 71 were canceled in an Amendment under 37 CFR § 1.116. New claims 77-94 were added in an Amendment and Response filed with a Request for Continued Examination filed on September 10, 2007. Claims 77-94 were cancelled in response to a Final Office Action mailed November 15, 2007. The amendments were entered in an Advisory Action dated February 7, 2008. The rejections of claims 1-14, 17, 67, 68, and 72 are being appealed herein.

The status of the claims is as follows:

A. Claims 1-6, 12-14, 17, 67, 68 and 72 stand erroneously rejected under § 103(a) as being unpatentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993).

B. Claims 7, 8 and 10 stand erroneously rejected under § 103(a) as being unpatentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), and Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991);

C. Claim 9 stands erroneously rejected under § 103(a) as being unpatentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as

evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991) as applied to claim 8 above, and further in view of Waggoner (US 5,268,486); and

D. Claim 11 stands erroneously rejected under § 103(a) as being unpatentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991) as applied to claim 1 above, and further in view of Ordahl (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976).

III. Grounds of Rejection to Be Reviewed on Appeal (37 C.F.R. § 41.37(c)(1)(vi))

A. Whether each of claims 1-6, 12-14, 17, 67, 68 and 72 is patentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993) where no proper *prima facie* case of obviousness has been established.

B. Whether each of claims 7, 8 and 10 is patentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), as applied to claim 1 above, and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991) where no proper *prima facie* case of obviousness has been established.

C. Whether claim 9 is patentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991) as applied to claim 8 above, and further in view of Waggoner (US 5,268,486) where no proper *prima facie* case of obviousness has been established.

D. Whether claim 11 is patentable over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730 A), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999) as evidenced by GibcoBRL Catalog (pages 18-15 ad 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993), in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1991) as applied to claim 1 above, and further in view of Ordahl (Nucl. Acids Res., vol. 3, pp. 2985-2999, 1976) where no proper *prima facie* case of obviousness has been established.

IV. Argument (37 C.F.R. § 41.37(c)(1)(vii))

The Examiner's final rejection of claims 1-14, 17, 67, 68, and 72 should be reversed in view of the following remarks submitted in furtherance of Appellant's Appeal Brief filed on May 5, 2008. Each of the claims, as presented, is allowable.

A. Claims 1-6, 12-14, 17, 67, 68 and 72 are Each Patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog, and Mackey

Claims 1-6, 12-14, 17, 67, 68 and 72 stand erroneously rejected under § 103(a) over Kallioniemi (US 2002/0132246 A1), McGill (US 5,658,730), Pollack (Nature Genetics, vol. 23, pp. 41-46, September 1999), in view of GibcoBRL Catalog (pp. 18-15 and 18-16, 1995-96) and Mackey (Anal. Biochem., vol. 212, pp. 428-435, 1993). These rejections are improper and should be reversed because the cited references do not render any of claims 1-6, 12-14, 17, 67, 68 and 72 obvious.

1. The Scope of the Term "About" is Clear in view of the Specification

It is improper to interpret the term "about" to mean any number of bases. (*See* page 2, lines 16-19 of the Final Office Action.) It is well established that terms such as "about" are interpreted with reference to what a person of ordinary skill in the art would understand in light of the specification. (*See* MPEP § 2173.05(b).) The meaning and scope of such terms are intended to be flexible and not only can but are intended to vary based on the context of their usage.

Under no situation would the term "about" be interpreted to include any number of bases as erroneously proffered. It is well established that "claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest reasonable interpretation'." (*In re Marosi*, 710 F.2d 799 at 802, 218 USPQ at 292 (quoting *In re Okuzawa*, 537 F.2d 545, 548, 190 USPQ 464,466 (CCPA 1976) (emphasis in original).) Appellants respectfully maintain that a reasonable interpretation of the term "about" does not include "any number of bases."

The Examiner is incorrect in asserting that, "what Appellant is arguing is that the meaning of the word "about" is defined by phrases which contain the word "about." (Examiner's Answer at page 12, part I.) On the contrary, Appellant exemplifies what ranges the phrase "smaller than about 200 bases" may include, *e.g.*, about 175 bases, about 150 bases, about 125 bases, about 100 bases, about 75 bases, about 50 bases, and so on to show that "about" does not mean "any number." (*See* specification, *e.g.*, at page 4, 1st paragraph; published application at paragraph no. [0010].) One of ordinary skill in the art would understand, for example from this context, that "about 175 bases" would encompass a certain range, while "about 150" would encompass a different range, both of these ranges being "smaller than about 200 bases." In view of these detailed examples, it is improper to interpret "about" to mean any number of bases.

2. Claims 1-6, 12-14, 17, 67, 68 and 72 are Patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog, and Mackey

Appellant disagrees that claims 1-6, 12-14, 17, 67, 68 and 72 would have been obvious to one of ordinary skill in the art over the Kallioniemi, McGill, and Pollack references, in view of the GibcoBRL Catalog and Mackey. The rejection is improper because no proper *prima facie* case of obviousness has been established.

There is no teaching, suggestion or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. (*See* MPEP § 2143, sub-section (G).) Moreover, even if proper evidence has been provided to establish a *prima facie* case of obviousness, any *prima facie* case of obviousness is rebutted because the teachings of Kallioniemi, McGill, Pollack, GibcoBRL Catalog and Mackey fail to disclose, teach or suggest the particular method as recited in claim 1.

One skilled in the art would not have been motivated to modify Kallioniemi or to combine Kallioniemi with any of the above citations. Kallioniemi does not disclose, teach or suggest a method that uses, in part, a plurality of immobilized nucleic acid

segments in an array that are a collection of clones that represent all of a chromosome or a genome of an organism, and contacting such probes with labeled fragments that include both strands of a double-stranded genomic DNA, as claimed by Appellants. Nor does the Examiner assert that this teaching is present in Kallioniemi.

Moreover, as acknowledged in the Examiner's Answer, Kallioniemi does not disclose, teach or suggest nucleic acid fragments with length of less than about 200 bp to less than about 30 bp or double-stranded DNA fragments labeled on both strands. (*See* Examiner's Answer at page 6, Part B and page 8, Part D.) Claim 1 recites that each genomic nucleic acid fragment consists of a length smaller than 200 bases, and that the labeled fragments include both strands of a double-stranded genomic DNA.

The above-noted deficiencies of Kallioniemi are not cured by any of the secondary citations. In addition, as described below in detail, the Examiner has not properly articulated a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the references. (*See* MPEP § 2143.)

McGill does not disclose, teach or suggest contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid, wherein said fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and wherein each labeled fragment consists of a length smaller than 200 bases. As described previously, McGill, at best, is ambiguous in describing the appropriate length for labeled fragments. McGill discloses different preferred or optimal labeled fragment lengths. For example, McGill generically states that, "it is contemplated that a nucleic acid fragment of almost any length.... For example, nucleic acid fragments may be prepared in accordance with the present invention which are up to 10,000 base pairs in length, with segments of 5,000 or 3,000 being preferred and segments of about 1,000 base pairs in length being particularly preferred." (McGill at col. 7, lines 31-40.) Thus, the teachings of McGill are contradictory as to what particular probe length is suitable. McGill also does not disclose labeling both strands of a double-stranded genomic DNA. McGill, either alone or in combination with Kallioniemi, does not render the method of claim 1 obvious.

Additionally, there no suggestion or motivation in McGill to combine McGill with Kallioniemi to arrive at the method of claim 1. One of ordinary skill in the art would not have been motivated to combine the ambivalent teaching of McGill with the teaching of Kallioniemi and arrive at the method of claim 1. No objective evidence has been provided that a person of ordinary skill in the art would be motivated to combine the molecular profiling method of Kallioniemi with the prostate cancer diagnostic techniques of McGill to arrive at Appellants' method of generating a molecular profile of genomic DNA. The Examiner's explanation (below) on the proposed motivation to combine the teachings of Kallioniemi and McGill does not provide objective evidence to a person of ordinary skill in the art so as to be motivated to combine the molecular profiling method of Kallioniemi with the prostate cancer diagnostic techniques of McGill. The Examiner's rationale in asserting that, "probes shorter than 200 bp... would anneal to a 20 bp sequence," is unclear, and the Examiner's assertion that, "binding of such probes will be very specific," is merely conclusory without giving any further clarification:

> Therefore, since the probes of McGill *et al.* are shorter than 200 bp, the result of using them in hybridization would be less probe aggregation and lower hybridization background, since each of the probes would anneal to a 20 bp sequence which appears once in 4^{20} bp in the genome or once every 1,099,511,627,776 bp in the genome (as compared to human genome size of 3,000,000,000 bp), that binding of such probes will be very specific, therefore reducing background and non-specific aggregation. (Examiner's Answer at page 20, part D).

It is also still unclear how the GibcoBRL Catalog combined with Pollack provides evidence that, "the labeling reaction would result in amplified double-stranded DNA with both strands labeled." (Examiner's Answer at page 8, part E.) Pollack does not disclose using labeled genomic nucleic acid smaller than about 200 bases. The GibcoBRL Calatong does not provide any disclosure that labeled fragments include both strands of a double-stranded genomic DNA, and there is no motivation in the references or identified by the Examiner to combine them. Therefore, even if Pollack and the GibcoBRL Catalog are properly combinable with Kallioniemi, the combination is still deficient and does not render claim 1 obvious because none of the references teach that <u>each</u> genomic nucleic acid fragment consists of a length <u>smaller than</u> 200 bases, and that the labeled fragments include <u>both</u> strands of a double-stranded genomic DNA.

With reference to the assertion that Mackey provides the motivation to "produce double-stranded labeled DNA fragments, in the method of Kallioniemi, McGill and Pollack (Examiner's Answer at page 8, part E), it is well accepted that the desirability of combining the cited references must exist in the cited references themselves. The mere fact that cited references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. (*KSR International Co v. Teleflex Inc.*, 550 U.S. __, __, 82 USPQ2d 1385, 1396 (2007); *see also* MPEP § 2143.01.)

Mackey and the GibcoBRL Catalog were cited by the Examiner for the sole purpose of labeling. It still remains unclear to Appellants how Mackey and the GibcoBRL Catalog, and therefore Pollack, teach labeling of both strands of genomic DNA. It is also unclear to Appellants how the passage by Mackey, cited by the Examiner is relevant to teaching labeling of both strands of DNA:

> In summary, the random primer biotin labeling system described here has a number of attractive features. Small amounts of template DNA (as little as 1 ng) can be amplified and labeled resulting in hundreds of nanograms to microgram of biotinylated probe. This amplification method is especially useful for labeling of DNAs which are difficult to isolate in large quantities; these include YACs, cosmids and DNA isolated from agarose and polyacrylamide gels. The probe size is small and is suitable for in situ hybridization procedures. (See Examiner's Answer at page 8, parte E, quoting Mackey at page 434, last paragraph.)

Because no suggestion or motivation exists, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Kallioniemi or to combine Kallioniemi with the secondary citations, as suggested by the Examiner, and because Kallioniemi, either alone or combination with the secondary citations, does not teach or suggest all the claim elements of claim 1, no *prima facie* case of obviousness has been established.

Claims 2-6, 12-14, 17, 67, 68 and 72, which depend directly or indirectly from independent claim 1, are patentable for at least the same reasons as claim 1.

In view of the above, 1-6, 12-14, 17, 67, 68 and 72 are patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog and Mackey.

B. Claims 7, 8 and 10 are Each Patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog, and Mackey, and further in view of Anderson

Claims 7, 8 and 10 stand erroneously rejected under § 103(a) over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog and Mackey and further in view of Anderson (Nucl. Acids Res., vol. 9, pp. 3015-3027, 1981).

As discussed above, Kallioniemi, either alone or in combination with any secondary citation, does not render claim 1 obvious. Because claims 7, 8 and 10 each depends directly or indirectly from claim 1, Kallioniemi, either alone or in combination with any secondary citations, does not render claims 7, 8 or 10 obvious, for at least the same reasons as discussed above.

In view of the above, no proper combination of cited references has been provided to render obvious the method of claim 7, which further defines the method of claim 1 by specifying that the sample of target genomic nucleic acid is prepared using a procedure such as random priming, nick translation, and amplification to generate segments of target genomic nucleic acid; followed by a step comprising fragmentation or enzymatic digestion, or both, to generate a sample of target genomic nucleic acid consisting of sizes smaller than 200 bases.

Similarly, claim 8 is not obvious in further defining the method of claim 7 by reciting that the random priming, nick translation, or amplification of target genomic nucleic acids incorporates detectably labeled base pairs into the segments.

Also, claim 10 is not obvious in that it further defines the method of claim 1 to comprise prior to step (b), the step of fragmenting the sample of target genomic nucleic acid to sizes smaller than about 200 bases by DNase enzyme digestion.

For argument's sake, even if some motivation or suggestion to combine the cited references does exist, Anderson still does not cure the deficiencies of Kallioniemi, McGill, Pollack, GibcoBRL or Mackey. Specifically, Anderson does not disclose fragmentation of target genomic DNA that has both strands labeled with a detectable moiety. Instead, the agarose gel shown in Figure 1 of Anderson was obtained by

digesting lambda DNA with DNase I. No evidence has been provided that both strands of the lambda DNA have been labeled.

In view of the above, claims 7, 8 and 10 are patentable over Kallioniemi, McGill, Pollack, in view of Gibco BRL Catalog and Mackey and further in view of Anderson.

C. Claim 9 is Patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog, and Mackey, in view of Anderson, and further in view of Waggoner

Claim 9 stands erroneously rejected under § 103(a) over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog and Mackey, in view of Anderson, and further in view of Waggoner (US 5,268,486).

As discussed above, Kallioniemi, either alone or in combination with any secondary cited reference, does not render claim 1 obvious. Because claim 9 depends indirectly from claim 1, Kallioniemi, either alone or in combination with any secondary reference, does not render claim 9 obvious, for at least the same reasons as those stated above.

For argument's sake, even if some suggestion or motivation to combine the cited references does exist, Waggoner still does not cure the deficiencies of Kallioniemi, McGill, Pollack, GibcoBRL or Mackey. Waggoner does not disclose labeling of both strands of genomic DNA and fragmentation or enzymatic digestion of the genomic DNA. Therefore, Waggoner's disclosure of Cy3 and Cy5 does not render claim 9 obvious.

In view of the above, claim 9 is patentable over Kallioniemi, McGill, Pollack, in view of Gibco BRL Catalog and Mackey, in view of Anderson, and further in view of Waggoner.

D. Claim 11 is Patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog, and Mackey, in view of Anderson, and further in view of Ordahl

Claim 11 stands erroneously rejected under § 103(a) over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog and Mackey, in view of Anderson, as applied to

claim 1 above, and further in view of Ordahl (Nucl. Acids Res., vol, 3, pp. 2985-2999, 1976).

Claim 11 depends indirectly from claim 1. As discussed above, Kallioniemi, either alone or in combination with any secondary cited reference, does not render claim 1 obvious. For at least the same reasons, Kallioniemi, either alone or in combination with any secondary cited reference, does not render claim 11 obvious.

Claim 11 further defines the method of claim 1 by reciting that prior to step (b) in claim 1, the step of fragmenting the sample of target genomic nucleic acid to sizes smaller than that about 200 bases is performed by applying shearing forces sufficient to fragment genomic DNA, followed by DNase enzyme digestion of the sheared DNA.

In addition to the above noted deficiencies, Ordahl is also deficient. Ordahl discloses a technique that produces DNA fragments of approximately 230 base pairs, whereas claim 11 recites fragmenting to produce sizes smaller than about 200 bases by shearing followed by enzymatic digestion of the sheared DNA with DNase.

The Examiner states that, "[t]he fragments created by Ordahl have an average size of 230 bp, which means that there are fragments shorter than 230 bp, but Anderson is used here to provide teaching and motivation to digest fragments to below 200 bp." (Examiner's Answer at pp. 26-27, part V.) However, neither of these references cures the deficiencies of the combination of references discussed above, e.g., no combination of these references teaches labeling of both strands of genomic DNA.

In view of the above, claim 11 is patentable over Kallioniemi, McGill, Pollack, in view of GibcoBRL Catalog and Mackey, in view of Anderson, as applied to claim 1 above, and further in view of Ordahl.

E. Conclusion

For the reasons provided above, each of the rejections is improper and should be reversed. Appellants respectfully request reversal of the rejections and issuance of a Notice of Allowance.

V. Claims Appendix (37 C.F.R. § 41.37(c)(1)(viii))

1. (Previously presented) A method for generating a molecular profile of genomic DNA by hybridization of a genomic DNA target to a plurality of immobilized nucleic acid probes, wherein the plurality is a collection of clones that represent all of a chromosome or a genome of an organism, the method comprising:

(a) providing the plurality of nucleic acid probes comprising a plurality of immobilized nucleic acid segments in an array with each probe at a known location, wherein each probe is a member of a genomic library cloned in a vector and each probe in the vector having a cloned nucleic acid insert greater than 50 kilobases, wherein the plurality of probes represents all of the chromosome or the genome;

(b) contacting the immobilized probes with a sample of target nucleic acid comprising fragments of genomic nucleic acid,

wherein said fragments include both strands of a double-stranded genomic DNA fragment and include at least 30% repetitive sequences, and

wherein both strands are labeled with a detectable moiety, wherein each labeled fragment consists of a length smaller than 200 bases, and the contacting is under conditions allowing specific hybridization of both strands of the labeled fragment of the target nucleic acid to the probe nucleic acid; and

(c) observing an amount and location of labeled genomic nucleic acid hybridized to each immobilized probe, to detect regions of amplification or deletion in the sample, wherein positional information of clones on the arrays and chromosomes is correlated,

wherein said method results in less aggregating hybridization to said probes relative to hybridization of said target genomic nucleic acid to said probes using target nucleic acids with labeled fragments of length greater than 200 bases,

or said method results in less background relative to hybridization of said target genomic nucleic acid using target nucleic acids with labeled fragments of length greater than 200 bases,

thereby generating a molecular profile of the chromosome or genome of the sample genomic nucleic acid.

2. (Previously presented) The method of claim 1, wherein each labeled fragment consists of a length no more than 150 bases.

3. (Previously presented) The method of claim 2, wherein each labeled fragment consists of a length no more than 100 bases.

4. (Previously presented) The method of claim 3, wherein each labeled fragment consists of a length no more than 50 bases.

5. (Previously presented) The method of claim 4, wherein each labeled fragment consists of a length no more than 30 bases.

6. (Previously presented) The method of claim 2, wherein each labeled fragment consists of a length between 30 bases and 150 bases.

7. (Previously presented) The method of claim 1, wherein the sample of target genomic nucleic acid is prepared using a procedure selected from the group consisting of random priming, nick translation, and amplification, of a sample of genomic nucleic acid to generate segments of target genomic nucleic acid; followed by a step comprising fragmentation or enzymatic digestion, or both, of the segments to generate a sample of target genomic nucleic acid consisting of sizes smaller than 200 bases.

8. (Previously presented) The method of claim 7, wherein the random priming, nick translation, or amplification, of the sample of genomic nucleic acid to generate segments of target genomic nucleic acid incorporates detectably labeled base pairs into the segments.

9. (Previously presented) The method of claim 8, wherein the detectable label comprises Cy3™ or Cy5™.

10. (Previously presented) The method of claim 1, further comprising prior to step (b), fragmenting the sample of target genomic nucleic acid to sizes smaller than about 200 bases by DNase enzyme digestion.

11. (Previously presented) The method of claim 1, further comprising prior to step (b), fragmenting the sample of target genomic nucleic acid to sizes smaller than about

200 bases by applying shearing forces sufficient to fragment genomic DNA followed by DNase enzyme digestion of the sheared DNA.

12. (Original) The method of claim 1, wherein the conditions allowing hybridization of the target nucleic acid to the probe nucleic acid comprise stringent hybridization conditions.

13. (Original) The method of claim 12, wherein the stringent hybridization conditions comprise a temperature of about 60°C to about 65°C.

14. (Original) The method of claim 1, wherein the target nucleic acid consists essentially of DNA derived from a human.

Claims 15-16 (cancelled)

17. (Previously presented) The method of claim 1, wherein the chromosome or genome is derived from a human.

Claims 18-66 (cancelled)

67. (Previously presented) The method of claim 72, wherein the sample of target genomic nucleic acid consists essentially of one chromosome.

68. (Previously presented) The method of claim 72, wherein the sample of target genomic nucleic acid comprises a complete genome.

Claims 69-71 (cancelled)

72. (Previously presented) The method of claim 1, wherein said fragments of genomic nucleic acid comprise nucleic acids from all of one or more chromosomes of said organism.

Claims 73-94 (cancelled)

VI. Conclusion

For the reasons provided above, the rejections are improper and should be reversed. Appellants respectfully request reversal of the rejections and issuance of a Notice of Allowance.

If there is any additional fee occasioned by this filing, including an extension fee that is not covered by an accompanying payment, please charge any deficiency to Deposit Account No. 50/2762, Ref. No. S2037-700210.

Respectfully submitted,
Allan Bradley et al, Appellants

/Sandra Szela Congdon/

Ann Lamport Hammitte, Reg. No. 34,858
Sandra Szela Congdon, Reg. No. 60,655
LOWRIE, LANDO & ANASTASI, LLP
Riverfront Office Park
One Main Street
Cambridge, MA 02142
Telephone: 617-395-7000
Facsimile: 617-395-7070

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